

Listing of Claims

This listing of claims replaces all previous listings of claims in the application.

1. (currently amended) A method of sequencing molecules of a polymer, comprising the steps of:
 - centering a fixed bias voltage across a pair of nano-electrodes separated by a channel therebetween, the bias voltage corresponding to an energy difference between any two internal energy levels of a molecule of interest;
 - modulating the bias voltage with a modulation waveform;
 - sequentially urging the molecules of a polymer comprised of linked molecules including at least one of the molecules of interest through the channel;
 - deriving an electrical signal indicative of the molecule of interest from tunneling current through the molecule of interest measured while the molecule of interest is between the nano-electrodes as the polymer passes through the channel; and
 - identifying the molecule of interest by comparing the derived electrical signal to known values of the signal for the molecule of interest.
2. (original) The method of claim 1, wherein the sequential urging step further comprises the step of funneling the polymer into the channel to restrict the passage of the polymer through the channel to a single molecule at a time.
3. (original) The method of claim 2, wherein the funneling step further comprises forcing the polymer through a nanopore or nanochannel.
4. (original) The method of claim 1, wherein the polymer is a nucleic acid.
5. (original) The method of claim 4, wherein the polymer is double-stranded DNA and the molecule of interest comprises a DNA base or a pair of DNA bases.

6. (original) The method of claim 4, wherein the polymer is single-stranded DNA and the molecule of interest comprises a DNA base.
7. (original) The method of claim 1, wherein the sequential urging step further comprises one of driving the polymer with an electric field, applying mechanical pressure to a solution in which the polymer is suspended, or directly manipulating the polymer with one or more pairs of optical tweezers.
8. (original) The method of claim 1, wherein the modulation waveform is selected from the group consisting of a sine wave, a sine wave wherein all harmonics of the sine wave are suppressed, a square wave, a synthetically generated waveform lacking an harmonic to be detected in the derived electrical signal, and a synthetically generated waveform that enhances at least one of the desired harmonics present in the derived electrical signal corresponding to the molecule of interest.
9. (original) The method of claim 1, wherein the step of deriving the characteristic electrical signal further comprises demodulating the tunneling current coherently with a demodulation waveform.
10. (original) The method of claim 9, wherein inelastic electron tunneling in the molecule exhibits a peak in the tunneling current demodulated with the second harmonic of the modulation waveform.
11. (original) The method of claim 9, wherein inelastic electron tunneling in the molecule exhibits a dispersion-like curve in the tunneling current demodulated with the third harmonic of the modulation waveform.
12. (original) The method of claim 9, wherein the demodulation waveform contains at least one of the following frequency components: the same frequency of the modulation waveform, all the sub-harmonics of the modulation waveform, and all the harmonics of the modulation waveform.

13. (original) The method of claim 9, further comprising the step of filtering of the tunneling current to improve the signal to noise ratio.
14. (original) The method of claim 9, wherein the deriving step further comprises extracting the signal from the demodulated tunneling current by filtering and/or post-processing.
15. (original) The method of claim 1, wherein the electrical signal comprises a resonance voltage determined from variations in tunneling conductance resolved from the tunneling current.
16. (original) The method of claim 15, wherein the bias voltage corresponds to the resonance voltage for the molecule of interest.
17. (original) The method of claim 1, further comprising:
 - centering at least one additional bias voltage across at least one additional pair of nano-electrodes separated by a channel so as to form at least one additional channel therebetween, the at least one additional bias voltage corresponding to the energy difference between any two internal energy levels of at least one additional molecule of interest;
 - modulating the at least one additional bias voltage with at least one additional modulation waveform;
 - urging the polymer through the at least one additional channel;
 - deriving at least one additional electrical signal indicative of the at least one additional molecule of interest from tunneling current between each respective pair of electrodes measured while a molecule portion of the polymer passes through the respective channel; and
 - identifying at least one additional molecule of interest by comparing the

respective derived electrical signals to known values of the signals for the molecules of interest by a single passage of the polymer through the channels.

18. (original) The method of claim 1, further comprising:
 - centering at least one additional bias voltage across at least one additional pair of nano-electrodes separated by a channel so as to form at least one additional channel therebetween, the at least one additional bias voltage corresponding to the energy difference between any two internal energy levels of the molecule of interest;
 - modulating the at least one additional bias voltage with at least one additional modulation waveform;
 - urging the polymer through the at least one additional channel;
 - deriving at least one additional electrical signal indicative of the molecule of interest from tunneling current between each respective pair of electrodes measured while a molecule portion of the polymer passes through the respective channel; and
 - further identifying the molecule of interest by comparing the respective derived electrical signals to known values of the signals for the molecules of interest by a single passage of the polymer through the channels.
19. (withdrawn) Method of identifying a characteristic electrical signal of a chemically known molecule, comprising the steps of:
 - positioning one or more chemically-known, identical molecules between a pair of nano-electrodes separated by a channel;
 - varying a bias voltage between the nano-electrodes across a voltage range encompassing the suspected internal energy level of the molecule;
 - modulating the bias voltage with a modulation waveform; and
 - deriving an electrical signal indicative of the one or more known molecule(s)

by analyzing and/or demodulating the tunneling current through the one or more molecules measured while the one or more known identical molecule(s) are positioned in the channel between the nano-electrodes.

20. (withdrawn) The method of claim 19, wherein the positioning step further comprises one of holding the one or more known molecules in the channel with one or more pairs of optical tweezers, or urging a polymer being comprised of the one or more identical molecules through the channel.
21. (withdrawn) The method of claim 19, wherein the positioning step further comprises applying and adjusting an electrophoretic driving voltage to a solution in which the one or more known molecules are suspended.
22. (currently amended) A system for sequencing molecules of a polymer, comprising:
 - a pair of nano-electrodes arranged to sequentially receive linked molecules of a polymer in solution in a channel formed therebetween;
 - a signal generator electrically connected to the nano-electrodes and configured to center a fixed bias voltage across the nano-electrodes corresponding to the energy difference between any two internal energy levels of a molecule of interest and to modulate the bias voltage with a modulation waveform;
 - means for urging the polymer through the channel;
 - means for measuring tunneling current between the nano-electrodes while a molecule portion of the polymer passes through the channel; and
 - signal processor for deriving an electrical signal indicative of the molecule of interest from the tunneling current and identifying the molecule of interest by comparing the derived electrical signal to known values of the electrical signal for the molecule of interest.

23. (original) The system of claim 22, further comprising means for restricting the passage of the polymer between the channel to a single molecule at a time.
24. (original) The system of claim 23, wherein the restricting means comprises a nanopore or nanochannel.
25. (original) The system of claim 22, wherein the urging means is selected from the group consisting of electrodes establishing an electric field applied to the solution, mechanical means creating a pressure gradient across the channel between the nano-electrodes, and one or more pairs of optical tweezers.
26. (original) The system of claim 22, wherein the modulation waveform lacks an harmonic to be detected in the derived electrical signal.
27. (original) The system of claim 22, wherein the modulation waveform enhances at least one of the desired harmonics present in the electrical signal corresponding to the molecule of interest.
28. (original) The system of claim 22, wherein the signal processor demodulates the tunneling current coherently with a demodulation waveform.
29. (original) The system of claim 28, wherein the demodulation waveform contains as least one of the following frequency components: the same frequency of the modulation waveform, all the sub-harmonics of the modulation waveform, and all the harmonics of the modulation waveform.
30. (original) The system of claim 28, further comprising one or more tunneling current filters for improving the signal to noise ratio prior to demodulation.

31. (original) The system of claim 22, wherein the electrical signal comprises a resonance voltage determined from variations in tunneling conductance resolved from the tunneling current.
32. (original) The system of claim 31, wherein the bias voltage corresponds to the resonance voltage for the molecule of interest.
33. (original) The system of claim 22, wherein the signal processor further comprises a data storage device for collecting and storing the derived electrical signals.
34. (original) The system of claim 33, wherein the signal processor is further arranged to access records of known electrical signals associated with molecules of interest stored in the data storage device for comparison to the derived electrical signals.